

II. REMARKS/ARGUMENTS

A. Status of Claims

Claims 38 and 47-52 are currently pending. Claims 1-37 and 39-46 were previously cancelled. Claim 38 has been amended herein. It is respectfully submitted that no new matter has been added by virtue of this amendment.

B. The Examiner's indication that the previous arguments are unpersuasive

The Examiner indicated that the previously submitted arguments were not persuasive. In response, Applicants will address the Examiner's reasons below:

I. Applicants arguments do comply with 37 CFR 1.111(b)

The Examiner has stated that "Applicants note that their claims contain 'consisting essentially of' language but fail to specifically point out how this limitation can be used to further distinguish the claimed invention from the prior art."

Initially, Applicants note that the present claims have been amended without prejudice to recite "consisting of" terminology with respect to the "analgesic" limitation. Accordingly, the present claims are "closed ended" with respect to this limitation and only encompass (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide (T-614) and/or salts thereof and (ii) oxycodone and/or salts thereof.

As discussed below, this limitation differentiates from the "NSAID" discussion in the Background of the Invention of Baker et al. (U.S. Patent No. 4,569,937), which is relied upon by the Examiner in rejecting the present claims.

II. Rejection under 35 U.S.C. 103 (a) over Baker et al. and Tanaka et al.

In the Office Action, the Examiner rejected claims 38, 47-48, 50-52 under 35 U.S.C. 103 (a) over US 4,569,937 (hereinafter "the Baker reference") and Tanaka et al. Arzneimittel-Forschung (1992) Vol. 42 (7) pages 935-44 (hereinafter "the Tanaka reference").

Applicants respectfully submit that the combination of cited references does not teach or suggest the presently claimed invention. The Baker reference does not teach or suggest the use of "NSAID's" and further does not contemplate any NSAID other than ibuprofen.

In the Office Action, the Examiner stated that "Baker et al. clearly teach the use of a general class of 'analgesic combinations' to relieve pain and reduce side effects that would otherwise be required by administration of the analgesic alone (e.g. See Baker et al. column 1, lines 12-17)."

Applicants respectfully point out that the Baker reference (column 1, lines 12-17) of recites:

More active analgesic combinations are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages thereby diminishing the expected side effects and toxicity that would result from the otherwise required higher dosages.

Applicants respectfully submit that this passage fails to teach or suggest the presently claimed analgesic combination.

Further, Applicants point out that the references to "NSAIDs" at column 1, lines 17-27, are the only recitations of the term "NSAID" in the Baker reference, and they are in reference to "a selected NSAID" of U.S. Patent No. 4,464,376 to Sunshine et al. (hereinafter "the Sunshine reference"). A copy of the Sunshine reference is attached hereto as Exhibit A. Applicants submit that the Sunshine reference disclosure is directed to combinations of caffeine and selected NSAIDs; caffeine and narcotic analgesics; and caffeine and selected NSAIDs/narcotic

analgesics. Applicants respectfully submit that the present claims are distinguished by the fact that they exclude the presence of caffeine by virtue of the "consisting of" terminology in the claims.

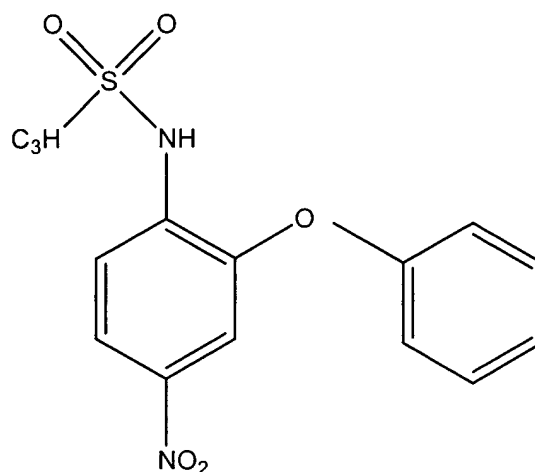
Furthermore, the Examiner's attention is directed to the Sunshine reference at column 14, lines 58-61, which recites "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove.**" (Emphasis added).

These five categories are set forth at column 7, lines 42-50 of the Sunshine reference as follows:

"The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives; and
- (5) the oxicams."

The chemical structures of these 5 categories are exemplified in the Sunshine reference at columns 8-11. Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide (shown below):



does not fall within any of the five structural categories indicated above. Therefore, even assuming *arguendo* that the Baker reference contemplates the use of other NSAIDs based on the reference to the Sunshine reference, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in the Sunshine reference and would not include N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide.

The Examiner further states:

The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is 'unexpectedly enhanced' or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting 'reduced dosages of narcotic analgesics' (e.g. oxycodone) AND which diminishes adverse side effect (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32.

Applicants respectfully point out that the mention of NSAIDs at column 1, as discussed above, is in reference to the Sunshine reference, which describes the enhanced analgesic effect resulting from the combination of any of the selected NSAIDs with caffeine. Also, as discussed

above, there is no mention of NSAIDs at column 2. Applicants further point out that column 3, lines 19-32, recites the following:

Application of an equieffective dose substitution model and a curvilinear regression analysis utilizing all the data for the individual compounds and various dose ratios for the combinations establishes the existence of unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen, i.e., the resulting activity is greater than the activity expected from the sum of the activities of the individual components.

As can be seen from the above cited passage, the Baker reference does not state that the enhanced analgesic activity occurs from "NSAID's such as ibuprofen", as improperly inferred by the Examiner, but rather solely from ibuprofen.

Further, Applicants submit that the Examiner has not shown any motivation to substitute N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide for ibuprofen. The Examiner states that "one of ordinary skill in the art would have been motivated to substitute N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide in the Baker compositions in light of the Tanaka reference teachings that ibuprofen [sic] is more analgesically potent with less side effects (e.g., as compared to ibuprofen in animal models)." However, one skilled in the art would not have been motivated to substitute the Baker formulations by substituting ibuprofen with any other NSAID, let alone N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, due to the purported unexpected results provided by ibuprofen. Moreover, the only NSAIDs alluded to in the Baker reference are the selected NSAIDs which fall into one of the five structural categories described in the Sunshine reference which do not include N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide.

Furthermore, Applicants submit that the Examiner is applying an improper "obvious to try" rationale in suggesting the substitution of ibuprofen with N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide. "In some cases, what would have been

'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Applicants submit that the present situation is analogous to *In re O'Farrell*, because one of ordinary skill in the art would have to test each one of the numerous possible NSAIDs in place of ibuprofen in order to arrive at the selection of N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, since the Baker reference gives no direction as to what NSAIDs other than ibuprofen would be successful.

The Examiner also stated that "the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, wherein the court held that it is *prima facie* obvious to combine two (or more) compositions which is taught by the prior art to be useful for the same purpose. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting T-614 for ibuprofen... " (emphasis added)(citations omitted).

Respectfully, Examiner's statements indicate that *In re Kerkoven* is not being properly applied in rejecting the present claims. As stated by the Examiner, the holding of *In re Kerkoven* is with respect to combining references. However, the Examiner's rejection is based on modifying the Baker analgesic composition. Applicants respectfully submit that a combination of the Baker analgesic composition with N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide would result in a formulation including a combination of N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and ibuprofen and an opioid analgesic which does not meet the "closed ended" limitation of the present claims with respect to the analgesic composition.

Applicants further submit that the Baker reference teaches away from the use of NSAIDs other than ibuprofen, based on the Baker reference's discussions of the synergistic

effect between ibuprofen and narcotic analgesics, and the absolute absence of any reference to other NSAIDs which may be used in the Baker formulation. In further support of this position, the Examiner is respectfully directed to column 1, lines 6 - 9 of the Baker reference, which states as follows:

This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals (emphasis added).

The Examiner is also directed to column 2, lines 11-15 of the Baker reference, which states as follows:

According to the present invention, there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,... (emphasis added).

Applicants further note that ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

In view of the above, one of ordinary skill in the art not be motivated to substitute the ibuprofen of the formulations of the Baker reference with N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide in view of the Tanaka reference. Further, Applicants submit that the Baker reference teaches away from the use of all other NSAIDs other than ibuprofen. Accordingly, it is respectfully requested that the 35 U.S.C. 103(a) rejection over the Baker and Tanaka references be removed.

C. Rejection under 35 U.S.C. 103 (a) over Baker et al. and Tanaka et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al. and Tanaka et al. in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.)

This rejection is traversed. It is respectfully submitted that the Oshlack references do not teach or suggest an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof. Accordingly, the Oshlack references fail to cure the deficiencies of the Baker reference in view of the Tanaka reference as set forth above.

Accordingly, it is respectfully requested that the 35 U.S.C. 103(a) rejection over the Baker, Tanaka and Oshlack references be removed.

III. CONCLUSION

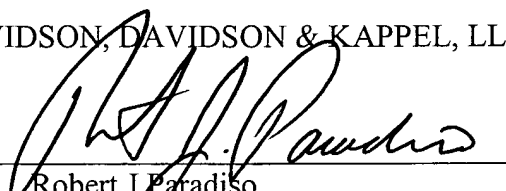
In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,

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